REMARKS

Formal Matters

Claims 136-154 and 156-159 are pending after entry of the amendments set forth herein.

The claims are not amended.

Reconsideration of this application is respectfully requested.

Drawings

The Examiner objects to Fig. 2 because the bars in the drawing allegedly cannot be clearly seen.

A replacement sheet for Fig. 2 is submitted herewith and it is believed that this objection has been addressed.

Withdrawal of this objection is requested.

Request for Interview

The Applicants submit that all rejections have been addressed by the arguments set forth below. If the arguments are not persuasive, the undersigned respectfully requests a telephonic interview with the Examiner to discuss possible claim amendments that would put the case in form for allowance. The undersigned is available by telephone at (650) 833 7723.

Rejection of claims under 35 U.S.C. § 112, first paragraph

Claims 136-143, 156 and 157 are rejected as not meeting the enablement requirement of 35 U.S.C. § 112, first paragraph. Applicants traverse.

As noted in the prior response, this rejection is based on the Examiner's contention that one of skill in the art would not be able to make and use active variants of RUP40 without undue experimentation.

In their prior response, the Applicants pointed out that the instant specification provides significant guidance for making active variants of RUP40, and also provided extrinsic evidence that RUP40 is a GPCR and therefore a member of an extremely well characterized family of proteins. The Applicants argued that given the information in the

instant specification and the deep general understanding of the structure and function of GPCR proteins, one of skill in the art would be able to make and use a large number of operable variants of RUP40 without undue experimentation. The Applicants prior arguments are preserved for appeal and not reiterated herein for the sake of brevity.

In this Office Action, the Examiner does not dispute the nature of the teachings of the instant specification. Rather, the Examiner dismisses the Applicants' prior arguments by stating that "Applicants' argument has been fully considered, but is not deemed to be persuasive because the human RUP40 set forth in SEQ ID NO:2 is not disclosed as being constitutively active and the 136 does not require that GPCR variants or homologues are constitutively active" (see paragraph bridging pages 4 and 5). As best understood by the Applicants from this paragraph, the Examiner believes that the claimed method can only be performed if: a) the GPCR used is constitutively active; or b) if an agonist for the receptor is used. Since neither is provided, the Examiner believes "one would have to determine first whether a particular GPCR [variant] can be used" in the method.

The Applicants submit that RUP40 does not have to be modified in order to be used in the assay to provide a phenotype. However, as explained in ¶553 of the specification (on page 133), RUP40 "manifested a level of constitutive Gq coupling activity" when used in the assay described in Example 14 of the application. As such, **the specification discloses that wild type RUP40 is constitutively active**. This conclusion is consistent with the results discussed in Example 15, which show that that wild type RUP40 causes a cellular phenotype if it is expressed in a cell. Thus, RUP40 does not need to be modified to become constitutively active in order for the claimed assay to work. The method may therefore be done without an agonist for the receptor, and without making a change to the receptor to make it constitutively active. Thus, the reason that the Examiner uses to dismiss this argument therefore lacks foundation.

Moreover, even if functional variants cannot be predicted with 100% accuracy by design alone, a functional variant can be readily identified by expressing the variant in a cell to determine if it has constitutive activity (see, e.g., Example 14) or causes a phenotype (see, e.g., Example 15). Such a method would not require undue experimentation. Rather, the

method would require routine experimentation of the type described in the many decisions cited in the Applicants' prior response.

Further, the Examiner states on page 5 that there is no nexus between (b) and (c). However, the same compound is used in both steps (b) and (c), and the claim is not directed to "two unrelated methods" as argued by the examiner. Rather, claim 136 is directed to a single method that has multiple steps, just like many (if not most) other method claims. The connection between steps (b) and (c) is clear in that the same compound is used in both of the steps.

In this Office Action, the Examiner further does not dispute the weight of the extrinsic evidence provided by the Applicants. Rather the Examiner dismisses the Applicants' prior arguments by stating that "The knowledge of structure/function relationship of GPCRs does not provide specific guidance of how to make a GPCR that can be used in the instant claimed method" (see page 6, 1st ¶).

The Applicants believe that the Examiner has missed the point that Applicants were trying to make in their last response. RUP40 is a GPCR and therefore a member of an extremely well characterized family of proteins. Restated in a different way, the point is that one of skill in the art can readily apply several years of scientific experience on the structure/function relationships in GPCRs to RUP40. For example and without any intent to limit the types of changes that could be made, since the transmembrane regions of a GPCR are well known to be hydrophobic and anchor the GPCR in a membrane, one of skill in the art would substitute one hydrophobic amino acid with another in a transmembrane region with a reasonable expectation that the GPCR would retain its capacity to signal. Likewise, based on what has been done on other GPCRs, a number of fusion proteins can be made using RUP40. None of this appears to have been disputed by the Examiner.

Moreover, even if functional variants cannot be predicted with 100% accuracy by design alone, functional variants can be identified by assaying a variant to determine if it has constitutive activity. This assay may be done using, for example, the methods described in Examples 14 or 15 of the instant application. Such a method would not require undue experimentation. Rather, the method would require routine experimentation of the type described in the decisions cited in the prior response.

Also, in the prior response, the Applicants argued that the claims recite functional language because they require "determining that the compound inhibits signaling by said G protein-coupled receptor". In this Office Action, the Examiner dismissed the argument by merely stating that "This is not persuasive for the reasons set forth above", which is understood to mean that this element, which requires that the GPCR used in the claimed method to be functional in the sense that it is capable of signaling, is not specific enough for the Examiner's liking.

To the extent that this part of the rejection has not been addressed by the foregoing discussion, the Applicants submit that there is no statutory requirement, Federal Circuit decision or U.S. guideline that specifically addresses the question of "how specific" a protein's function need be recited in a claim that recites a genus of related proteins. To the Applicants' knowledge, the most relevant recent decision with precedence is *In re Kubin*, which is discussed in the Applicants' prior response. While *In re Kubin* does not address "how specific" a protein's function need be recited, it does reiterate that the enablement requirement can be met even if extensive experimentation is required to practice a claim.

In this Office Action, the Applicants' arguments regarding the Board of Appeals decisions of *Ex Parte Kubin*, *Ex parte Liao*, *Ex parte Heck* and *Ex parte Abad* were summarily dismissed because the fact pattern in the instant case is different to those discussed in those decisions. In essence, the Examiner states that the instant claims do not contain a "meaningful" functional limitation and, as such, there is no parallel between the instant cases and the cases described in the decisions. However, the Applicants submit that "determining that the compound inhibits signaling by said G protein-coupled receptor" provides a meaningful functional limitation in that RUP40 is protein that is involved in signal transduction, and moreover the specification provides details of the downstream molecular events that are effected by RUP40 signaling (see, e.g., ¶14 on page 4, ¶553 on page 133 and Fig. 5). As such, the Applicants believe that the claims offer a meaningful functional limitation.

Further, on page 7 of the Office Action, the Examiner states that the "the specification does not disclose and Applicants do not explain how to identify an antagonist of the human RUP40 that inhibits hypertrophy in heart without a known ligand/agonist". This has been

addressed in detail at least in part in the prior response and above. Stated again, **Example 14 of the instant application demonstrates that wild type RUP40 manifests constitutive Gq coupling activity.** As taught in ¶328 of the specification (on page 69), agonists encompass "materials not previously known to activate the intracellular response when they bind to the receptor" (e.g., "to elevate intracellular IP3 level"). The specification throughout teaches how to screen for agonists of human RUP40 (see, e.g., ¶9 on page 3, ¶¶94-96 on page 22, ¶103 on page 23, and ¶328 on page 69); for example, by way of exemplification the specification teaches elevation of intracellular IP3 by an agonist of human RUP40 (see, e.g., ¶14 on page 4, ¶533 on page 133 and Fig. 5). As such, in contrast to the Examiner's assertion, the specification *does* disclose how to identify an antagonist of the human RUP40 that inhibits hypertrophy in heart cells without a known ligand/agonist.

Finally, on page 8 Examiner states that Example 15 on page 133 of the instant specification "does not provide a valid example with respect to how to identify an inhibitor that inhibits hypertrophy in a heart cell". Applicants don't understand what the Examiner means by this comment. Example 15 describes an example in which RUP40 is overexpressed in cultured cells (NRVMs; neonatal rat ventricular monocytes) that are an accepted *in vitro* model for cardiac hypertrophy and heart failure *in vivo*. Since overexpression of RUP40 causes hypertrophy in an accepted model of cardiac hypertrophy and heart failure *in vivo*, the Applicants do not understand why Example 15 is not a "valid" example of how an inhibitor that inhibits hypertrophy in a heart cell can be identified.

Rejection of claims under 35 U.S.C § 112, 2nd ¶

Claims 136-143 and 155 to 157 are rejected under 35 U.S.C § 112, second paragraph, as indefinite because claim 136 does not have a preamble.

The Applicants submit that claim 136 does recite the term "A method" prior to transitional term "comprising" in the claim. As such, claim 136 does contain a preamble.

Moreover, there is no statutory or judicial requirement for a claim preamble to recite the purpose or intended use of a claim, which is what the examiner appears to require for claim 136. If this rejection is to be maintained, the Examiner is kindly requested to cite an

authority that requires that a preamble state more than the statutory class to which an invention belongs. Otherwise, this rejection should be withdrawn.

The Applicants submit that this rejection has been adequately addressed and may be withdrawn. Withdrawal of this rejection is respectfully requested.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number AREN-060.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: April 27, 2010

By: /James S. Keddie, Reg. No. 48,920/
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Enclosures: Formalized Fig. 2

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